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(54) **Pharmaceutical compositions containing non-steroidal anti-inflammatory agents**

(57) The invention relates to a pharmaceutical composition comprising a systemic non-steroidal anti-inflammatory drug together with the histamine H_2-antagonist ranitidine or a physiologically acceptable salt thereof. The histamine H_2-antagonist reduces gastric mucosal lesions caused by the anti-inflammatory drug.

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SPECIFICATION

Pharmaceutical compositions

This invention relates to improvements in the formulation of anti-inflammatory drugs.

Systemic non-steroidal anti-inflammatory drugs, such as aspirin, indomethacin and ibuprofen, are known to give rise to undesirable side effects. In particular, they are known to be ulcerogenic and can thus, for example, give rise to gastric ulceration when administered orally. This side effect may be further enhanced in combination with other factors such as stress. Since in some treatments these compounds may have to be used for an extended period, such side effects can prove a serious disadvantage.

Ranitidine is the approved name for N-[2-[[[5-(dimethylamino)methyl]-2-furanyl]methyl]thio]ethyl-N'-methyl-2-nitro-1,1-ethenediamine which is described and claimed in British Patent Specification 1,565,966. It is a potent histamine H_2-antagonist which may be used in the treatment of conditions where there is an advantage in lowering gastric acidity, particularly in gastric and peptic ulceration, and in the treatment of allergic and inflammatory conditions where histamine is a known mediator. It has now been discovered that mucosal lesions of the gastrointestinal tract caused by systemic non-steroidal anti-inflammatory drugs can be significantly reduced by co-administering ranitidine.

The present invention provides a pharmaceutical composition comprising a systemic non-steroidal anti-inflammatory drug ad ranitidine or a physiologically acceptable salt thereof.

Particularly useful pharmaceutical compositions according to the invention are those in a form suitable for oral or rectal administration.

The systemic non-steroidal anti-inflammatory drugs which may be employed in the invention generally also show analgesic activity and include, for example, aspirin, indomethacin, ibuprofen, fenoprofen, ketoprofen, naproxen, mefenamic acid, diflunisal, benorylate, azapropazone, diclofenac, fenbufen, fepra-zone, fenclofenac, flufenamic acid, flurbiprofen, oxyphenbutazone, phenylbutazone, piroxicam, sulindac and tolmetin. They may be used in the pharmaceutical compositions of the invention in their usual dosage amounts, e.g. 50mg - 1 g of aspirin, 10 - 100mg of indomethacin and 100 - 500mg of ibuprofen per dosage unit taken one or more times daily in accordance with the normal dosage regime for the drug in question.

It is preferred that ranitidine should be employed in the composition in the form of a physiologically acceptable salt. Such salts include salts of inorganic or organic acids such as the hydrochloride, hydrobromide, sulphate, acetate, maleate, succinate and fumarate salts. The hydrochloride salt is particularly preferred. The amount of ranitidine, preferably in the form a physiologically acceptable salt, employed in the pharmaceutical composition of the invention will be an amount sufficient to reduce the gastrointestinal distress caused by the anti-inflammatory drug and will preferably be in the range of 10 - 200mg per dosage unit.

The pharmaceutical compositions of the invention may be presented in a conventional manner with the aid of at least one pharmaceutical carrier or excipient. The composition may take the form of, for example, tablets, capsules, powders, granules, solutions, syrups, suspensions, or suppositories, prepared by conventional means with acceptable excipients. The composition may thus contain as excipients, for example, binding agents, compression aids, fillers, lubricants, disintegrants and wetting agents. If desired, other active ingredients may also be present in such compositions. Tablets may be coated in conventional manner, for example, with a suitable film-forming material such as methyl cellulose, ethyl cellulose and/or hydroxypropylmethyl cellulose or with sugar. Liquid preparations may also contain, for example, edible oils such as peanut oil. Suppositories may contain, for example, fat-soluble or water miscible bases.

The pharmaceutical compositions of the invention may be prepared according to conventional techniques well known in the pharmaceutical industry. Thus, for example, the anti-inflammatory drug and the ranitidine or ranitidine salt may be admixed together, if desired, with suitable excipients. Tablets may be prepared, for example, by direct compression of such a mixture. Capsules may be prepared by filling the blend along with suitable excipients into gelatin capsules, using a suitable filling machine.

Alternatively, the pharmaceutical compositions of the invention may be presented in a suitable controlled release form so that the ranitidine or its salt is rapidly made available for absorption and the non-steroidal anti-inflammatory drug is released more slowly. The pharmaceutical compositions may thus be presented for oral or rectal administration in a conventional manner associated with controlled release forms.

The pharmaceutical compositions of the invention maybe used in the treatment of inflammatory conditions, particularly acute and chronic musculo-skeletal inflammatory conditions such as rheumatoid and osteoarthritis and ankylosing spondylitis, and for analgesia in conditions such as dysmenorrhoea, especially where the use of the anti-inflammatory drug is limited by gastro-intenstinal side-effects.

In order that the invention may be more fully understood, the following Examples are given by way of illustration only.

Example 1 - TABLETS

(a)		mg/tablet
	Ranitidine hydrochloride	168.00*
	Ibuprofen	400.00
	Lactose	387.00
	Hydroxypropyl methylcellulose	5.00
	Sodium starch glycollate	30.00
	Magnesium stearate	10.00
	Compressive weight	1000.00

*Equivalent to 150 mg ranitidine base

The ranitidine hydrochloride and ibuprofen are sieved through a 250 μm sieve and blended with the lactose. This mix is granulated with a solution of the hydroxypropyl methylcellulose. The granules are dried, screened and blended with the sodium starch glycollate and the magnesium stearate. The lubricated granules are compressed into tablets using 12.5mm punches.

(b)		mg/tablet
	Ranitidine hydrochloride	168.00
	Indomethacin	50.00
	Microcrystalline cellulose	79.00
	Magnesium stearate	3.00
	Compression weight	300.00

The ranitidine hydrochloride and indomethacin are blended with the microcrystalline cellulose and magnesium stearate and compressed using 9.5mm punches.

Example 2 - CAPSULES

(a)		capsule
	Ranitidine hydrochloride	168.00
	Ibuprofen	400.00
	Starch 1500**	228.00
	Magnesium stearate	4.00
	Fill weight	800.00

** A form of directly compressible starch supplied by Colorcon Ltd, Orpington, Kent.

The ranitidine hydrochloride and ibuprofen are sieved through a 250 μm sieve and blended with the Starch 1500 and magnesium stearate. The resultant mix is filled into size 0 hard gelatin capsules using a suitable filling machine.

(b)		mg/capsule
	Ranitidine hydrochloride	168.00
	Indomethacin	50.00
	Starch 1500	80.50
	Magnesium stearate	1.50
	Fill weight	300.00

The ranitidine hydrochloride and indomethacin are sieved through a 250 μm sieve and blended with the Starch 1500 and magnesium stearate. The resultant mix is filled into size 2 hard gelatin capsules using a suitable filling machine.

CLAIMS

1. A pharmaceutical composition comprising a systemic non-steroidal anti-inflammatory drug and ranitidine or a physiologically acceptable salt thereof.
2. A phrarmaceutical composition as claimed in claim 1 in which the anti-inflammatory drug is aspirin, indomethacin, ibuprofen, fenoprofen, ketoprofen, naproxen, mefenamic acid, diflunisal, benorylate, azapropazone, diclofenac, fenbufen, feprazone, fenclofenac, flufenamic acid, flurbiprofen, oxyphenbutazone, phenylbutazone, piroxicam, sulindac or tolmetin.
3. A pharamaceutical composition as claimed in claim 1 or 2, also including at least one pharmaceutical carrier or excipient.
4. A pharmaceutical composition as claimed in any of claims 1 to 3 in a form suitable for oral or rectal administration.
5. A pharmaceutical composition as claimed in claim 4 in which the anti-inflammatory drug is indomethacin or ibuprofen.
6. A pharmaceutical composition as claimed in claim 5 which contains 10 - 100 mg of indomethacin or 100 - 500 mg of ibuprofen per dosage unit and 10 - 200 mg of ranitidine or a physiologically acceptable salt thereof per dosage unit.
7. A pharmaceutical composition as claimed in any of claims 1 to 6 in which the ranitidine is used in the form of the hydrochloride salt.

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